The impact of influenza viruses on hospitalizations in infants younger than two years old during epidemics of respiratory syncytial virus infection

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In order to evaluate the association of influenza viruses with hospitalizations for acute respiratory infection in infants younger than two years old during epidemics of respiratory syncytial virus infection, we studied 512 nasal washes from this population. The samples were obtained from 1997 to 2000. A total of 337 viruses were isolated: 264 respiratory syncytial viruses, 62 influenza viruses, eight parainfluenza viruses, two adenovirus and one rhinovirus. Hospitalizations for acute respiratory infection were owing to influenza and respiratory syncytial viruses in 18.3% vs. 78.3% of all cases, and 32.5% vs. 65.8%, respectively, in the group of infants between 6 months and 2 years old.

Keywords Respiratory syncytial virus, influenza virus, pediatric respiratory infection

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INTRODUCTION

The implication of influenza viruses in hospitalizations of children under 2 years old is unclear because the interpretation has been confused by the simultaneous occurrence of epidemics of respiratory syncytial virus (RSV). This is the major cause of lower respiratory tract infections in developed countries among this population [1–6]. It carries an increased risk of serious complications among infants with underlying conditions such as cardiovascular diseases and cystic fibrosis [7–9]. Vaccination against the influenza virus is well-documented as the primary method for preventing complications and reducing the severity of the disease caused by the influenza virus infection [10]. Recently, it has been suggested that children should be vaccinated, because several studies have demonstrated influenza-related hospitalizations for respiratory complications among this group [11–14].

Our objective was to evaluate the association of influenza and respiratory syncytial virus infections with hospitalizations for respiratory disease among infants younger than two years old when epidemics of both viruses coincide.

MATERIALS AND METHODS

We studied simultaneous winter epidemics of influenza virus and RSV during three seasons from 1997 to 2000. Epidemiological data on influenza epidemics were obtained from the Andalusian Influenza Surveillance Network and data on the RSV circulation were assessed by isolation of the virus in respiratory samples from infants attending the Hospital Universitario Virgen de las Nieves, during the three seasons. Co-circulation of the influenza virus and RSV ranged from weeks 3–11 of 1998 (period 1), from weeks 50 in 1998 to 11 in 1999 (period 2), and from weeks 53 in 1999 to 9 in 2000 (period 3). Influenza epidemics coincided with the RSV circulation during the three periods. However, RSV was detected in December 1997 (one month earlier than the beginning of the influenza epidemic of period 1) and in March 2000 (one month later than the influenza epidemic of period 3).

In order to evaluate the association of the influenza A virus and RSV epidemics with hospitalizations for acute respiratory infection (ARI) in infants younger than 2 years old, we analyzed the total and ARI monthly hospitalizations among

this group in our hospital from May 1997 to May 2000.

All infants younger than 2 years old and who were hospitalized for ARI in our hospital during the three periods were included in the study ($n = 512$), 179 of whom (35%) were 6 months to 2 years old. Neither the infants nor their mothers had previously received vaccination against influenza viruses. A total of 512 nasal washes from these patients (148 in period 1, 230 in period 2 and 134 in period 3) were obtained and processed for virological procedures within 12 h of reception.

Respiratory viruses isolation was carried out by a previously described method following the inoculation of samples into simultaneous culture of Hep-2, MDCK and LLC-MK2 cells by a shell-vial assay [15] and human embryonic lung fibroblast cells (MRC-5) by traditional tube culture.

The RSV, influenza A and B virus, parainfluenza 1, 2 and 3 viruses, and adenovirus were identified by direct immunofluorescence (IMAGEN, Dako Diagnostics Ltd, Cambridgeshire, UK), and the rhinovirus and enterovirus grown in the MRC-5 tube culture were identified by physical-chemical tests, i.e. sensitivity to 5-bromo-2′-deoxyuridine, pH 3 and chloroform.

Influenza A virus isolations were subtyped by an indirect immunofluorescence with monoclonal antibodies against H1 and H3 hemagglutinins (Light Diagnostic, CHEMICON International Inc., CA, USA).

Statistical results of the mean duration of hospitalizations during the periods with and without simultaneous influenza virus and RSV epidemics were analyzed by the Student's *t*-test.

RESULTS

A total of 337 viral isolations were obtained (65.8% of all the samples analyzed). The results of viral isolations are shown in Table 1. RSV was isolated in 51.56% of the samples from the three periods, influenza A and B viruses in 12.1% and other viruses in 2.14%. Influenza A viruses were subtyped as H3 in periods 1 and 2, and as H3 ($n = 19$) and H1 ($n = 8$) in period 3.

If only the RSV and influenza viruses are taken into account, positive cultures were obtained in 211 infants younger than 6 months during the three periods, 187 of whom had RSV and 24 had influenza viruses (88.6% vs. 11.4%). The same viruses were isolated from 115 infants between 6 months and 2 years old, 77 being RSV and 38 influenza viruses (67% vs. 33%).

A total of 759 infants younger than 2 years old were hospitalized during the three periods, 512 (67.4%) being as a result of ARI: 216 hospitalizations in period 1, 302 in period 2 and 241 in period 3, of which 148, 230 and 134 were as a result of ARI, respectively.

The mean number of hospitalizations in infants younger than 2 years old during the months with and without cocirculation of RSV and influenza-

Table 1 Isolation of respiratory viruses during three periods of simultaneous respiratory syncytial virus (RSV) and influenza virus epidemics

	Simultaneous RSV and influenza virus epidemics				
	Period 1[a]	Period 2[b]	Period 3[c]	Total	6 months to 2 years[d]
Samples	148	230	134	512	179
Virus isolation	89	145	103	337	117
RSV	80 (89.9)[e]	112 (77.2)	72 (69.9)	264 (78.3)	77 (65.8)
Influenza A	7 (7.8)	18 (12.4)	27 (26.2)	52 (15.4)	31 (26.5)
Influenza B	1 (1.1)	9 (6.2)	–	10 (2.9)	7 (6)
Parainfluenza 1	–	–	1 (0.9)	1 (0.3)	0 (0)
Parainfluenza 2	–	2 (1.4)	–	2 (0.6)	0 (0)
Parainfluenza 3	–	3 (2)	2 (1.9)	5 (1.5)	1 (0.8)
Adenovirus	1 (1.1)	1 (0.6)	–	2 (0.6)	1 (0.8)
Rhinovirus	–	–	1 (0.9)	1 (0.3)	0

[a]Period 1, from week 3–11, 1998.
[b]Period 2, from week 50 1998 to week 11 1999.
[c]Period 3, from week 53 1999 to week 9 2000.
[d]group of infants between 6 months and 2 years old.
[e]*n* (% respect to viruses isolation).

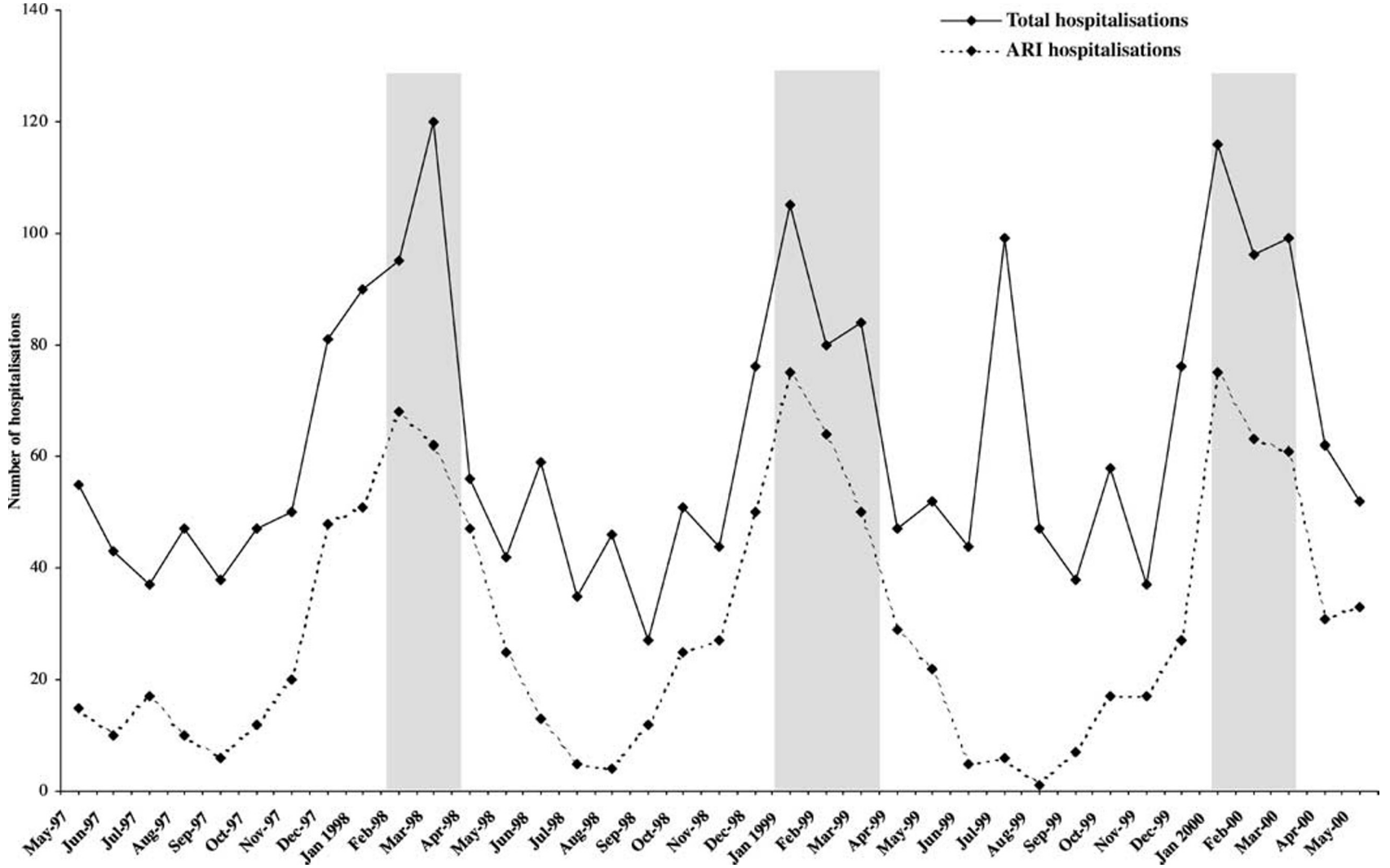

Figure 1 Total and acute respiratory infection (ARI) hospitalizations in infants younger than 2 years. Simultaneous epidemics of influenza and respiratory syncytial virus are highlighted in the gray columns.

related epidemics was 93.8 ± 15.8 and 51.6 ± 17.2, respectively ($P < 0.05$), which yields an increase in hospitalizations of 77.3% during epidemics, mainly owing to ARI (Figure 1).

As the results of viral isolations demonstrate (Table 1), RSV and influenza viruses are responsible for 78.3% (range: 69.6–89.8%) and 18.3% (range: 10–26.2%) hospitalizations owing to ARI, respectively, in periods of simultaneous epidemics of both viruses. If only infants between 6 months and 2 years old are taken into account, the RSV and influenza viruses were responsible for 65.8% and 32.5% of hospitalizations, respectively.

DISCUSSION

RSV and influenza virus epidemics usually coincide during winter seasons in temperate climates. Although RSV is considered the principal cause of ARI in infants younger than 2 years old, the association with the increase of hospitalizations for ARI during simultaneous RSV and influenza virus epidemics is not still clear.

Recent studies [12,13] have reported an increase of hospitalizations in infants younger than 2 years old during influenza-related epidemics that might justify the systematic vaccination of this population, although they eliminate the possible effect of RSV by epidemiological data but not by viral isolations.

Our results are similar to those reported by other authors who studied the etiology of ARI in a pediatric population when the RSV and influenza virus coincide and demonstrate that RSV isolations are higher than those of influenza virus in all population groups and especially in infants younger than 2 years old in whom RSV is up to two-fold greater than that of influenza virus isolations [6].

The results obtained in our study also show a preponderance of RSV over influenza A and B isolations in infants younger than 2 years old admitted to hospital for ARI, when epidemics owing to both viruses coincide. However, 61.3% of influenza viruses isolations corresponded to infants between 6 months and 2 years old, susceptible to influenza vaccination, which yields 32.5% hospitalizations in this group vs. 11.4% in infants younger than 6 months.

Thus, our results support the possible beneficial effect of vaccination of the pediatric population, as recently recommended [10], although the decision to vaccinate against influenza viruses also depends on several other factors that have not been evaluated in this work, such as the number of influenza-associated hospitalizations relative to other vaccine preventable diseases and the cost-effectiveness of different vaccine alternatives.

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